Intravenous Nutrition

A Clinical Evaluation of a 50 Per Cent Dextrose in Water Solution, Containing 1 mg. of Hydrocortisone per 100 ml.

RAYMOND E. WESTON, *M.D., Ph.D.*, and
S. JEROME PORT, *M.D.*, Beverly Hills

• **A 50 per cent dextrose in water solution, containing 1 mg. of hydrocortisone per 100 ml., was used successfully in 70 patients for intravenous nutritional maintenance and repletion. There were no adverse systemic effects during or following 216 infusions. The only undesirable local reaction was the rare occurrence of pain in the arm when the concentrated solutions were given too rapidly. Glycosuria was minimal if the infusion rate did not exceed 0.85 gm. of glucose per kilogram of body weight per hour, particularly if 50 units of insulin were added to each 550 ml. bottle of 50 per cent dextrose. In patients without significantly elevated serum potassium content, 30 mEq. of potassium chloride, acetate or phosphate was added to each bottle to prevent hypokalemia.**

Preliminary observations suggest that this new solution may be given safely intravenously, without need for cutdowns or plastic catheters, if the needle is carefully inserted and well immobilized in the arm vein and the duration of the infusion is not too prolonged. Further studies on the effect of such high caloric supplementation plus protein hydrolysates in parenteral nutritional repletion and maintenance are indicated.

WITH THE PARENTERAL SOLUTIONS and supplements now available, it is possible to treat, prophylactically or actively, most of the common fluid and electrolyte aberrations. However, the severe malnutrition that complicates acute and chronic illness and is often associated with hyponatremia and intracellular potassium depletion, still presents a therapeutic challenge. The major problem is to provide sufficient calories, in addition to protein hydrolysates and electrolytes, to promote repletion of the depleted tissues without administration of excessive fluid to patients who often are already overhydrated, as Moore has emphasized.[12] Unfortunately, concentrated glucose solutions given by intravenous needle, usually produce severe phlebitis and often thrombosis.[16] Therefore, highly concentrated dextrose solutions have not been given intravenously except, as in patients with acute renal failure, via plastic catheters threaded through extremity veins into the vena cava.[18]

Recently, McNair and Dudley[10] emphasized the dangers of thrombophlebitis following this practice, or of septicemia if there is severe infection elsewhere in the body. Moncrief[11] and Hassall and Rountree[7] reported similar clinical experiences. Bogen[2] recently observed that complications developed at the site of the cutdown in 14.5 per cent of 234 cases.

To provide calories without these hazards, fat emulsions for intravenous administration have been developed. Unfortunately, after a few days even the best of these produce febrile or other systemic reactions.[9,13]

Some of the factors contributing to local phlebitis and thrombosis following intravenous infusions, as well as possible prophylactic measures, were investigated by McNair and Dudley[10] who drew the following conclusions:

1. The infusion site plays a role, since significant phlebitis occurred much more frequently in the long saphenous or other leg veins than in arm veins.

2. Venipuncture *per se* is not important because intravenous needles, carefully inserted and well immobilized in forearm veins for as long as 72 hours, produced negligible local trauma.

3. The pH of the solution is not significant, for heat-sterilized dextrose solutions produced no more venous irritation than did filter-sterilized solutions containing less acid.

4. Local clotting may not be of primary importance, since addition of 200 units of heparin per 100 ml. did not reduce the incidence of thrombophlebitis following experimental infusions of more than 24 hours' duration.

5. Local tissue reaction to prolonged infusion was significantly reduced by adding 1 mg. of hydrocortisone per 100 ml. of solution infused.

Polak[15] had previously reported that three patients in hepatic coma showed no clinical evidence of thrombophlebitis during or following infusions of 20 per cent dextrose solution, containing 1 mg. of hydrocortisone per 100 ml., for 32 to 63½ hours. More recently, he and his colleagues[6] reported that

From the Department of Medicine, Cedars of Lebanon Hospital, Los Angeles 29.

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TABLE 1.—*Sex and Age Range of Patients*

Sex	Number	Range in Age, Years
Males	33	23 to 84
Females	37	27 to 89

TABLE 2.—*Clinical Data on Patients*

Clinical Diagnoses	Number of Patients
Carcinoma	18
Cardiovascular disease	9
Hepatic disease	9
Blood dyscrasias	8
Uremia	6
Peptic ulcer	6
Ulcerative colitis	5
Renal shut down	2
Miscellaneous	7
Total	70

TABLE 3.—*Frequency of Administration of 50 Per Cent Dextrose and Water Solution with Hydrocortisone*

Number of Administrations	Number of Patients	Number of Bottles
1	26	26
2	15	30
3	9	27
4	7	28
5	3	15
6	4	24
7	1	7
8	1	8
10	1	10
13	1	13
14	2	28
Totals	70	216

TABLE 4.—*Mode of Administration of Infusions*

Mode of Administration	Number of Patients	Number of Infusions
Intravenous needle	53	150
Intravenous catheter	7	30
Cutdown catheter	6	24
Needle or cutdown	4	12*
Total	70	216

*20 Intravenous infusions included in I.V. needle column.

in a larger, well controlled series this concentration of hydrocortisone had no effect on the incidence or severity of the local reaction to intravenous infusions administered for more than 24 hours. The latter observation confirmed the reports of Horwitz, Sachar, and Elman[8] and of Carter[3] that the duration of infusion is of prime importance in the pathogenesis of infusion thrombophlebitis.

The present report is concerned with the use of the anti-inflammatory properties of hydrocortisone to reduce the incidence of infusion phlebitis following administration of concentrated dextrose solutions. The data suggest that a solution of 50 per cent dextrose in water, containing 1 mg. of hydrocortisone per 100 ml.,* may be infused slowly with an intravenous needle, without significant local or systemic reaction. As much as 750 gm. of dextrose per day may be given intravenously in only 1,500 ml. of solution without use of a plastic catheter or venous cutdown.

METHODS AND MATERIALS

Tables 1 and 2 summarize the pertinent clinical and statistical data on 70 subjects. The majority were patients at the Cedars of Lebanon Hospital, but some were seen in consultation at other hospitals in Los Angeles. A total of 216 infusions were given with individual patients receiving from one to fourteen infusions (Table 3). In 53 patients the infusions were administered intravenously with an 18- or 20-gauge needle (Table 4). In seven an in-dwelling polyethylene catheter was threaded through a needle into the vein. In six patients intravenous cutdown was done, generally on a branch of the long saphenous vein. In four patients infusions were given through needles and cutdowns. Thirty-six of the 216 infusions were given through a cutdown or an intravenous catheter.

Although infusions were given more rapidly, at times, to test the patient's subjective and metabolic response to the resulting hyperglycemia, generally the rate was adjusted to provide less than the 0.85 gm. of dextrose per kg. of body weight per hour, which generally may be given to a normal person without producing significant glycosuria.[5] Thus, in four hours a 70 kg. subject would be given 550 ml. of 50 per cent dextrose solution containing 1 mg. of hydrocortisone per 100 ml. Most normal subjects were able to metabolize the 250 gm. of dextrose per bottle with little or no glycosuria. However, to reduce the strain on the beta cells of the islets of Langerhans,[1] 50 units of regular insulin (one unit per 5 gm. of dextrose) usually was added to each 550 ml. bottle. To promote more rapid hepatic deposition of glycogen and potassium in patients with hyperpotassemia, 100 units of regular insulin was added to the first bottle of 50 per cent dextrose solution given each day, and 50 units was added to each subsequent bottle. The total fluid replacement requirements of patients in acute renal failure (estimated from insensible loss plus losses in urine, stool and vomitus) were supplied quantitatively with the concentrated dextrose solution. The 600 to 750 gm. of glucose per day provided sufficient calories to reduce decidedly the breakdown of tissue for energy production.

*Supplied as Molidex by Don Baxter, Inc., Glendale, California.

To each bottle given to patients without hyperkalemia, 30 mEq. of potassium phosphate, chloride or acetate was added, the specific anion being determined by the patient's clinical requirements. In addition, supplements of vitamin B complex, vitamins K and C, magnesium sulfate and calcium gluconate were given, as indicated.

Many of the surgical or malnourished patients were provided with approximately 2,800 calories per day by the following schedules:

1. An initial four-hour infusion of 550 ml. of 50 per cent dextrose with hydrocortisone, containing 50 units of regular insulin, 30 mEq. of potassium phosphate, plus vitamins.

2. A five-hour infusion of 1,050 ml. of a 10 per cent casein hydrolysate (Hyprotigen®) solution containing 7.5 per cent ethyl alcohol, 1 mg. of hydrocortisone per 100 ml., 33 mEq. of potassium, and 84 mEq. of sodium, with 8.2 mEq. of added magnesium sulfate.

3. A final four-hour infusion of 550 ml. of the first solution, containing 8.2 mEq. of magnesium sulfate and 30 mEq. of potassium chloride or potassium acetate, depending on patient's acid-base requirement.

Whenever possible, infusions were given through needles carefully placed into a large vein in the arm. The site of the infusion was inspected frequently to permit correction of faulty placement of the needle or to note any irritation or thrombosis of the vein or infiltration around the vein. After the last infusion was completed, the needle was carefully withdrawn and light pressure exerted at the site of the puncture for several minutes with the patient's arm elevated and the forearm extended. Alternate arms were used on successive days, the available adequate veins being used in rotation. The patients were carefully observed and examined during and 24 hours after each infusion. Any subjective complaints or objective findings were recorded.

Serum electrolytes, blood sugar, and daily urinary dextrose excretions were determined by standard methods on a number of subjects. Pulse, temperature, and often blood pressure were recorded every four hours during and following most infusions.

RESULTS

A total of 216 infusions were given to the 70 patients (Table 3).

In the 53 patients in whom administration was through a needle, no significant local or systemic reactions were observed. The only complaint recorded (Table 5) was of pain at the site of infusion or along the course of the vein when the infusion rate was too rapid or the vein too small to permit adequate dilution of the decidedly hypertonic solution. In only two instances was the pain severe enough to necessitate discontinuing the infusion. Occasionally, there was some transient soreness at the infusion site. However, in no case did thrombosis or even persistent phlebitis ensue.

TABLE 5.—*Patient Reactions to Infusions*

Patient	Subjective Complaint	Subsequent Thrombosis or Phlebitis
1.	Local pain during 2 of 3 infusions	None
2.	Pain during infusion	None
3.	Pain during infusion	None
4.	Pain radiating to shoulder	None
5.	Initial pain stopped when infusion was slowed	None
6.	Severe pain requiring cessation of infusion into small vein	None
7.	Pain during 1st hour of 1 of 5 infusions	None
8.	Pain during more rapid infusion	None
9.	Local pain during 1 of 14 infusions	None
10.	Severe local pain requiring cessation of infusion	None
11.	Initial pain stopped when infusion was slowed	None
12.	Initial pain stopped when infusion was slowed	None
13.	Pain in arm after one-liter infusion	None

In seven agitated or restless patients, the needle slipped out of the vein with resulting subcutaneous infiltration of the 50 per cent dextrose solution with hydrocortisone. However, no inflammation, infection or slough resulted, the only evidence of local reactions being areas of painless ecchymosis.

In contrast, in three of four 550 ml. intravenous infusions of ordinary 50 per cent dextrose in water solution without hydrocortisone there was local pain, thrombosis and phlebitis which subsided uneventfully but obliterated the affected vein.

In seven patients with in-dwelling polyethylene catheters, and in the ten with intravenous cutdown, phlebitis and thrombosis of the veins ultimately developed. Although the house officers felt the vessels tended to remain open longer than ordinarily in patients receiving the 50 per cent dextrose with hydrocortisone solutions, a much larger series will be needed before such a conclusion can be statistically verified.

Hyperglycemia and Glycosuria

In patients given single slow infusions of 50 per cent dextrose with hydrocortisone solutions without insulin, blood sugar content increased only 70 to 200 mg. per 100 cc. Consequently, only 3 to 16 gm. of dextrose per 24 hours was excreted in the urine. Subsequent infusions produced similar patterns of glycosuria. However, when 50 units of regular insulin was added to each 550 ml. of solution, blood sugar rose less and generally only 2 to 3 gm. of dextrose per day was excreted in the urine even after a number of daily infusions. In patients with either severe hepatic disease or uremia, blood sugar levels tended to be higher, even when insulin was added to the infusion.

TABLE 6.—*Changes in Chemical Contents of Serum and Blood During Treatment of a Uremic Acidotic Hyperkalemic Patient*

Day	Serum Electrolytes (mEq. per liter) K	CO_2	Na	Cl	Blood Urea Nitrogen mg. per 100 cc.	Creatinine mg. per 100 cc.	Hemoglobin gm. per 100 cc.
1 (Pre-treatment)	7.9	10.5	140	117	88	9.7	8.1
2	5.9	15.0	140	112	76	9.5	....
3	4.6	17.0	....	....	....	....	....
4	4.1	25	140	110	62	9.0	9.4

Electrolyte Changes

Continued infusions without added potassium salts, especially with insulin supplements, were associated with decreases in serum potassium. For example, in one malnourished woman the serum potassium fell to 2.7 mEq. after one infusion and rose slowly when 30 mEq. of potassium phosphate was added to each subsequent bottle. No other significant changes in serum electrolytes were noted, probably because appropriate sodium, calcium and magnesium salts were added, as indicated above, for patients who were receiving all their nutrition parenterally.

Uremia with Acidosis and Hyperkalemia

In uremic and other hyperkalemic patients, serum potassium levels fell promptly and progressively following infusions of 50 per cent dextrose with hydrocortisone. Table 4 presents data on a typical patient, a 32-year-old man with uremia resulting from a congenitally fused kidney and chronic pyelonephritis. On admission, he appeared moribund, having severe oliguria, respirations of 65 per minute due to pronounced acidosis, and the blood contents typical of severe uremia, acidosis and hyperkalemia (Table 6). He was given a four-hour infusion of 550 ml. of 50 per cent dextrose in water with hydrocortisone, supplemented with 100 units of regular insulin and 90 mEq. of sodium lactate, followed by an infusion of 1,000 ml. of 10 per cent dextrose in water, supplemented with vitamins B and C, 40 units of regular insulin and 90 mEq. of sodium lactate. By the next morning, serum potassium had fallen from 7.2 to 5.9 mEq. per liter and the carbon dioxide content rose from 10.5 to 15.0 mEq. per liter. That day another liter of the augmented 10 per cent dextrose in water was given, preceded and followed by 550 ml. infusions of the 50 per cent dextrose with hydrocortisone plus insulin and sodium lactate, and the serum electrolyte situation improved further. The next day only one 550 ml. bottle of the concentrated dextrose with hydrocortisone was given, followed by two units of blood and a liter of the augmented 10 per cent dextrose in water solution. By the following day, when the patient was well enough to be discharged home, the electrolyte contents were essentially normal.

Effects of Hydrocortisone

No evidence of any adverse effects of small amounts of hydrocortisone administered were observed in any patients. The largest daily dose was only 21.5 mg. when two bottles of the concentrated dextrose solution and one liter of the supplemented protein hydrolysate solution were given.

CLINICAL RESPONSE

In patients with chronic uremia or acute renal failure, the clinical response was excellent with rapid correction of hyperkalemia and acidosis and lowering of the blood urea nitrogen content. In malnourished patients, even those with metastatic malignant disease, improvement was noted following the increased caloric and nitrogen intake. After five or six days of vigorous parenteral nutrition, many patients regained appetite, began to eat and showed pronounced increase in vigor. No adverse clinical responses were observed.

It should be noted that, although this report deals only with 216 infusions, almost 500 bottles of 50 per cent dextrose with hydrocortisone have been administered at this hospital. The present series includes only those cases in which adequate observations were made. However, no significant reactions other than occasional transitory local soreness have been noted in the larger series. Moreover, the use of the new solution on all the clinical services has been steadily and spontaneously increasing, whenever adequate parenteral nutrition is needed.

DISCUSSION AND CONCLUSIONS

The present data demonstrate that properly prepared 50 per cent dextrose in water solutions, containing 1 mg. of hydrocortisone per 100 ml., may be given intravenously through an ordinary needle at a rate providing 0.85 gm. of dextrose per kg. of body weight per hour, without significant local or systemic reaction. Although limited control studies tend to confirm the widespread clinical impression that similar administration of 50 per cent dextrose solutions without hydrocortisone generally produces decided venous irritation, and often phlebitis or thrombosis or both, a larger control series is neces-

sary to provide statistical support for this conclusion. However, the resulting discomfort and danger to the patients made it difficult to justify the continued use of the control solutions in this study, particularly in view of the therapeutic success being achieved with the solutions containing 0.001 per cent hydrocortisone.

Fortunately, the maximal rate of infusion associated with minimal glycosuria is well tolerated by most patients. However, at times an even slower rate may be required to avert local pain due to the hypertonicity of the solution. To reduce venous irritation, the 20 or 22-gauge needle should be carefully inserted in a large vein in the arm, firmly immobilized, and removed in less than 15 hours. The duration of infusion, particularly, must be carefully controlled, as has been emphasized by many investigators.[3,6,8,10,16]

Despite these limitations of rate and duration of administration, it has been possible, in 13 or 14 hours, to give infusions providing 550 gm. of dextrose, 100 gm. of casein hydrolysate, 75 ml. of ethyl alcohol, 93 mEq. of potassium, 84 mEq. of sodium, and 16.4 mEq. of magnesium in a total volume of 2,150 ml. containing only 21.5 mg. of hydrocortisone. Such parenteral therapy, supplying protein hydrolysate and electrolytes plus 2,800 calories in only 2,150 ml. of solution, will not only adequately maintain well-nourished medical and surgical patients but may also permit repletion of severely malnourished subjects by promoting utilization of the nitrogen administered.

As emphasized by Pareira and Somogyi[14] and Spencer and Beal,[19] improved appetite often follows intravenous administration of sufficient dextrose to correct the ketosis of starvation. This factor plus the increased vigor following partial nutritional repletion may explain the decided improvement in oral intake observed in many patients in the present series after five or six days of adequate parenteral therapy. Wider application of these solutions is required to determine if the anticipated salubrious effect on the morbidity following extensive gastrointestinal operations, trauma, burns, comatose states and other debilitating clinical conditions will be achieved.[12,16,19]

In patients with acute renal failure, infusion of 1,000 to 1,500 ml. of concentrated dextrose with 0.001 per cent hydrocortisone and the proper amount of insulin not only provides sufficient calories for metabolic maintenance, thereby reducing tissue breakdown, but also promotes deposition of potassium with glycogen, thus decreasing hyperkalemia. Preferably, the infusion should be given intermittently, alternating veins from arm to arm. If continuous infusion is needed, a different vein should be used every 12 to 14 hours. As Salisbury[17] recently noted, metabolism in profoundly uremic patients may be so distorted, at times, as to impair utilization of carbohydrate. In these circumstances concentrated dextrose infusions may produce increasing hyperglycemia which is unaffected by concurrent administration of large doses of insulin.

As indicated above, a larger control series will be required to determine whether properly prepared 50 per cent dextrose solutions without hydrocortisone may be given without venous trauma if the precautions described in this study are taken. Spencer and Beal[19] reported that phlebitis was uncommon following infusion of 25 per cent dextrose plus 5 per cent alcohol in water solutions through a 22-gauge needle carefully placed in a vein. They suggested that perhaps the hazard of phlebitis due to infusions of hypertonic dextrose solutions has been overemphasized in the past. However, the absence of significant local reaction to accidental subcutaneous infiltration of the 50 per cent dextrose solutions with hydrocortisone is consistent with the anticipated anti-inflammatory properties of the steroid.[15] It is in striking contrast to the local redness and soreness following subcutaneous infiltration of other solutions without hydrocortisone.[16] The failure of the steroid to reduce the incidence of phlebitis and thrombosis following infusions of more than 24 and 48 hours' duration[6] is not surprising. Under these conditions, the time-intensity factor probably far exceeds the physiological-pharmacological potential of the hydrocortisone.

In conclusion it should be reemphasized that these observations are preliminary. However, the results observed in this and in other[4] clinics suggest that 50 per cent dextrose in water solution, containing 1 mg. of hydrocortisone per 100 ml., may be given intravenously to provide calories in a limited fluid volume. Further studies on the clinical and metabolic effects of such treatment in the management of patients with acute and chronic renal failure, and for nutritional maintenance or repletion of medical patients, as well as surgical patients, preoperatively and postoperatively, are in progress.

435 North Bedford Drive, Beverly Hills (Weston).

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